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DATE: Thursday, October 21, 2004

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		DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR	
☐	L30	L29	9
		DB=PGPB,USPT; PLUR=YES; OP=OR	
☐	L29	briand-jacques.in.	9
☐	L28	L11 and L27	0
☐	L27	(enzyme and product) with NMR	118
☐	L26	5804390.pn. or 5698401.pn.	2
☐	L25	5804390.pn	0
☐	L24	isotop$ and l19	1
☐	L23	(1H or 3H or 11B or 13C or 15N or 19F or 29S or 31P) and L22	0
☐	L22	L21	1
☐	L21	chemical adj shift and L19	1
☐	L20	chemical ajd shift and L19	898333
☐	L19	20030143757.pn.	1
		DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR	
☐	L18	6150179.pn.	2
		DB=USPT; PLUR=YES; OP=OR	
☐	L17	6150179.pn.	1
		DB=EPAB; PLUR=YES; OP=OR	
☐	L16	WO-9857155-A1.did.	1
☐	L15	WO-9857155-A1.did.	1
		DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR	
☐	L14	L13 not l10	1
☐	L13	L11 and L12	5
☐	L12	(substrate or ligand) with NMR	1730
☐	L11	NMR with (one adj dimension$ adj spectr$ or two adj dimension$ adj spectr$ or three adj dimension$ adj spectr$)	35
		DB=PGPB,USPT; PLUR=YES; OP=OR	
☐	L10	L7 and L9	4
☐	L9	NMR with (one adj dimension$ adj spectr$ or two adj dimension$ adj spectr$ or three adj dimension$ adj spectr$)	29
☐	L8	L5 and L7	238

☐	L7	(substrate or ligand) with NMR	1579
☐	L6	l2 and L5	355
☐	L5	NMR with (one adj dimension$ or two adj dimension$ or three adj dimension$)	2019
☐	L4	NMR same (one adj dimension$ or two adj dimension$ or three adj dimension$)	3112
☐	L3	l1 AND L2	1303
☐	L2	(substrate or ligand) same NMR	4300
☐	L1	NMR and (one adj dimension$ or two adj dimension$ or three adj dimension$)	12089

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                  resulting in a closer connection to BABS
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                  fields
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 NEWS  9  SEP 01  INPADOC: New family current-awareness alert (SDI) available
 NEWS 10  SEP 01  New pricing for the Save Answers for SciFinder Wizard within
                  STN Express with Discover!
 NEWS 11  SEP 01  New display format, HITSTR, available in WPIDS/WPINDEX/WPIX
 NEWS 12  SEP 27  STANDARDS will no longer be available on STN
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               AND CURRENT DISCOVER FILE IS DATED 11 AUGUST 2004
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=> file medline biosis embase caplus wpids
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                                                   ENTRY    SESSION
FULL ESTIMATED COST                                 0.21       0.21
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=> s nmr and (substrate or ligand or product)
L1       86252 NMR AND (SUBSTRATE OR LIGAND OR PRODUCT)

=> s nmr and (substrate or ligand or enzyme)
L2       64621 NMR AND (SUBSTRATE OR LIGAND OR ENZYME)

=> s l1 and l2
L3       49788 L1 AND L2

=> e briand jacques/in
'IN' IS NOT A VALID EXPAND FIELD CODE FOR FILE 'MEDLINE'
'IN' IS NOT A VALID EXPAND FIELD CODE FOR FILE 'EMBASE'
E1           1     BRIAND J M/IN
E2          20     BRIAND J P/IN
E3           4 --> BRIAND JACQUES/IN
E4           1     BRIAND JEAN/IN
E5           1     BRIAND JEAN J/IN
E6          19     BRIAND JEAN PAUL/IN
E7           3     BRIAND JEAN PIERRE/IN
E8           8     BRIAND L/IN
E9           3     BRIAND L E/IN
E10          1     BRIAND LAETITIA/IN
E11          3     BRIAND LAURA E/IN
E12          1     BRIAND LOIC/IN
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=> e briand jacques/au
E1         579     BRIAND J P/AU
E2           1     BRIAND J Y/AU
E3          24 --> BRIAND JACQUES/AU
E4           1     BRIAND JEAN/AU
E5           1     BRIAND JEAN CLAUDE/AU
E6          11     BRIAND JEAN FRANCOIS/AU
E7           1     BRIAND JEAN J/AU
E8          11     BRIAND JEAN P/AU
E9         305     BRIAND JEAN PAUL/AU
E10         27     BRIAND JEAN PIERRE/AU
E11         12     BRIAND JOEL/AU
E12         18     BRIAND K/AU

=> s e3
L4          24 "BRIAND JACQUES"/AU
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=> s l4 and l1
L5            3 L4 AND L1

=> dup rem
ENTER L# LIST OR (END):l5
PROCESSING COMPLETED FOR L5
L6            2 DUP REM L5 (1 DUPLICATE REMOVED)

=> t ti l6 1-2

L6   ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2004 ACS on STN
TI   Mechanism of Inhibition of Cathepsin K by Potent, Selective
     1,5-Diacylcarbohydrazides: A New Class of Mechanism-Based Inhibitors of
     Thiol Proteases

L6   ANSWER 2 OF 2  BIOSIS  COPYRIGHT (c) 2004 The Thomson Corporation.  on STN
     DUPLICATE 1
TI   Design of potent and selective human cathepsin K inhibitors that span the
     active site.


=> d ibib abl l6 1-2
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=> d ibib abs l6 1-2

L6   ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:         1999:709526  CAPLUS
DOCUMENT NUMBER:          132:44920
TITLE:                    Mechanism of Inhibition of Cathepsin K by Potent,
                          Selective 1,5-Diacylcarbohydrazides: A New Class of
                          Mechanism-Based Inhibitors of Thiol Proteases
AUTHOR(S):                Bossard, Mary J.; Tomaszek, Thaddeus A.; Levy, Mark
                          A.; Ijames, Carl F.; Huddleston, Michael J.;
                          Briand, Jacques; Thompson, Scott; Halpert,
                          Stacie; Veber, Daniel F.; Carr, Steven A.; Meek,
                          Thomas D.; Tew, David G.
CORPORATE SOURCE:         Departments of Molecular Recognition Physical and
                          Structural Chemistry and Medicinal Chemistry,
                          SmithKline Beecham Pharmaceuticals, King of Prussia,
                          PA, 19406, USA
SOURCE:                   Biochemistry (1999), 38(48), 15893-15902
                          CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER:                American Chemical Society
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   The nature of the inhibition of thiol proteases by a new class of
     mechanism-based inhibitors, 1,5-diacylcarbohydrazides, is described.
     These potent, time-dependent, active-site spanning inhibitors include
     compds. that are selective for cathepsin K, a cysteine protease unique to
     osteoclasts.  The 1,5-diacylcarbohydrazides are slow substrates for
     members of the papain superfamily with inhibition resulting from slow
     enzyme decarbamylation.  Enzyme-catalyzed hydrolysis of
     2,2'-N,N'-bis(benzyloxycarbonyl)-L-leucinylcarbohydrazide is accompanied
     by formation of a hydrazide-containing product and a carbamyl-enzyme
     intermediate that is sufficiently stable to be observed by mass spectrometry
     and NMR.  Stopped-flow studies yield a saturation limited value of 43
```

s-1 for the rate of cathepsin K acylation by 2,2'-N,N'-bis(benzyloxycarbonyl)-L-leucinylcarbohydrazide. Inhibition potency varies among proteases tested as reflected by 2-3 orders of magnitude differences in Ki and kobs/I, but all eventually form the same stable covalent intermediate. Reactivation rates are equivalent for all enzymes tested (1 + 10-4 s-1), indicating hydrolysis of a common carbamyl-enzyme form. **NMR** spectroscopic studies with cathepsin K and 2,2'-N,N'-bis(benzyloxycarbonyl)-L-leucinylcarbohydrazide provide evidence of inhibitor cleavage to generate a covalent carbamyl-enzyme intermediate rather than a tetrahedral complex. The **product** Cbz-Leu-hydrazide does not appear enzyme-bound after cleavage in the **NMR** spectra, suggesting that the stable inhibited form of the enzyme is the thioester complex. 1,5-Diacylcarbohydrazides represent a new class of unreactive cysteine protease inhibitors that share a common mechanism of action across members of the papain superfamily. Both S and S' subsite interactions are exploited in achieving high selectivity and potency.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 2 OF 2 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
DUPLICATE 1

ACCESSION NUMBER: 1998:82491 BIOSIS
DOCUMENT NUMBER: PREV199800082491
TITLE: Design of potent and selective human cathepsin K inhibitors that span the active site.
AUTHOR(S): Thompson, Scott K.; Halbert, Stacie M.; Bossard, Mary J.; Tomaszek, Thaddeus A.; Levy, Mark A.; Zhao, Baoguang; Smith, Ward W.; Abdel-Meguid, Sherin S.; Janson, Cheryl A.; D'Alessio, Karla J.; McQueney, Michael S.; Amegadzie, Bernard Y.; Hanning, Charles R.; Desjarlais, Renee L.; **Briand, Jacques**; Sarkar, Susanta K.; Huddleston, Michael J.; Ijames, Carl F.; Carr, Steven A.; Garnes, Keith T.; Shu, Art; Heys, J. Richard; Bradbeer, Jeremy; Zembryki, Denise; Lee-Rykaczewski, Liz; James, Ian E.; Lark, Michael W.; Drake, Fred H.; Gowen, Maxine; Gleason, John G.; Veber, Daniel F. [Reprint author]
CORPORATE SOURCE: Dep. Medicinal Chem., SmithKline Beecham Pharm., 709 Swedeland Road, P.O. Box 1539, King Prussia, PA 19406, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (Dec. 23, 1997) Vol. 94, No. 26, pp. 14249-14254. print.
CODEN: PNASA6. ISSN: 0027-8424.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Feb 1998
Last Updated on STN: 24 Feb 1998

AB Potent and selective active-site-spanning inhibitors have been designed for cathepsin K, a cysteine protease unique to osteoclasts. They act by mechanisms that involve tight binding intermediates, potentially on a hydrolytic pathway. X-ray crystallographic, MS, **NMR** spectroscopic, and kinetic studies of the mechanisms of inhibition indicate that different intermediates or transition states are being represented that are dependent on the conditions of measurement and the specific groups flanking the carbonyl in the inhibitor. The species observed crystallographically are most consistent with tetrahedral intermediates that may be close approximations of those that occur during **substrate** hydrolysis. Initial kinetic studies suggest the possibility of irreversible and reversible active-site modification. Representative inhibitors have demonstrated antiresorptive activity both in vitro and in vivo and therefore are promising leads for therapeutic agents for the treatment of osteoporosis. Expansion of these inhibitor

concepts can be envisioned for the many other cysteine proteases implicated for therapeutic intervention.

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=> d his

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     FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS, WPIDS' ENTERED AT 12:02:06 ON 21
     OCT 2004
L1         86252 S NMR AND (SUBSTRATE OR LIGAND OR PRODUCT)
L2         64621 S NMR AND (SUBSTRATE OR LIGAND OR ENZYME)
L3         49788 S L1 AND L2
                 E BRIAND JACQUES/IN
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L4            24 S E3
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